PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/50, 47/36, 9/16, 9/20, 9/28, 9/48 — A1

(11) International Publication Number: **WO 99/55337**

(43) International Publication Date: 4 November 1999 (04.11.99)

(21) International Application Number: PCT/FI99/00331

(22) International Filing Date: 23 April 1999 (23.04.99)

(30) Priority Data:
980902 23 April 1998 (23.04.98) FI

(71) Applicant *(for all designated States except US)*: ORION CORPORATION [FI/FI]; Orionintie 1, FIN–02200 Espoo (FI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LARMA, Ilkka [FI/FI]; Orion–yhtymä Oyj, PI 65, FIN–02101 Espoo (FI). HARJULA, Maarit [FI/FI]; Lehtisaarentie 6 B, FIN–00340 Helsinki (FI).

(74) Agent: ORION CORPORATION; Orion Pharma, Industrial Property Rights, P.O. Box 65, FIN–02101 Espoo (FI).

(81) Designated States: AE, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: STABILE COMPOSITIONS COMPRISING LEVOSIMENDAN AND ALGINIC ACID

(57) Abstract

The present invention relates to pharmaceutical compositions of levosimendan comprising alginic acid for improving the stability of levosimendan in the compositions. Levosimendan is useful in the treatment of congestive heart failure.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

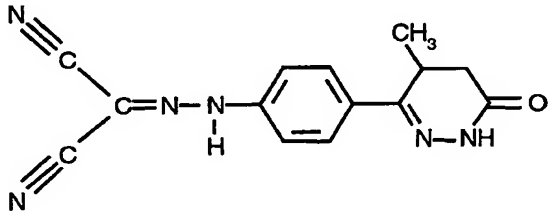
STABILE COMPOSITIONS COMPRISING LEVOSIMENDAN AND ALGINIC ACID

Technical field

The present invention relates to pharmaceutical compositions, particularly for oral administration, with improved stability comprising levosimendan, the (-) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile, as the active ingredient. Levosimendan is useful in the treatment of congestive heart failure.

Background of the invention

Levosimendan, which is the (-)-enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, and the method for its preparation is described in EP 565546 B1. Levosimendan is potent in the treatment of heart failure and has significant calcium dependent binding to troponin. Levosimendan is represented by the formula:



I

The hemodynamic effects of levosimendan in man are described in Sundberg, S. et al., Am. J. Cardiol., 1995; 75: 1061-1066. Pharmacokinetics of levosimendan in man after i.v. and oral dosing is described in Sandell, E.-P. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S57-S62, 1995. The use of levosimendan in the treatment of myocardial ischemia is described in WO 93/21921. Clinical studies have confirmed the beneficial effects of levosimendan in heart failure patients.

The preparation of pharmaceutical compositions of levosimendan, particularly for oral use, has proved to be difficult. When combined with conventional excipients levosimendan shows poor stability and easily degrades under storage conditions. Therefore, there is a need for pharmaceutical preparations of levosimendan which show improved stability of the active ingredient under storage.

Summary of the invention

It has now been unexpectedly found that alginic acid significantly improves the stability of levosimendan in pharmaceutical compositions.

Thus the present invention provides a pharmaceutical composition of levosimendan, particularly for oral administration, with improved stability comprising alginic acid as a stability improving agent.

Detailed description

The compositions of the invention comprise generally about 0.1 - 99 % of alginic acid per weight of the composition. More typically, a composition of the invention comprises about 5 - 70 %, preferably about 10 - 40 %, of alginic acid per weight of the composition.

Typically, the composition of the invention is for oral administration. Such compositions include solid compositions in the form of e.g. tablets, dragees, capsules, powders and granules. The contents of the active compound in the composition of the invention is generally from about 0.01 to 100 %, preferably from 0.1 to 20 %, most preferably from 0.5 to 10 % per weight. In general levosimendan is administered orally to man in doses from about 0.1 to 10 mg, preferably from 0.5 to 5 mg once or several times a day depending on the age, body weight and condition of the patient.

In addition to levosimendan and alginic acid the composition of the invention may comprise pharmaceutically acceptable carriers and excipients. Pharmaceutically acceptable carriers and excipients include those which are used according to standard pharmaceutical practice and which are compatible with the active ingredient. For oral administration in tablet form, suitable carriers and excipients include microcrystalline cellulose such as Avicel PH101, lactose, corn starch, magnesium stearate, stearic acid, calcium phosphate and talc. For oral administration in capsule form, useful carriers and excipients include micro-crystalline cellulose, lactose, corn starch, magnesium stearate, stearic acid and talc. Capsules can be prepared by mixing the active ingredient with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatine capsules. Tablets can be prepared by mixing the active ingredient with the carriers and excipients and compressing the powdery mixture into tablets.

The composition may be designed to release the active ingredient rapidly or in a controlled/extended fashion. Typically long-acting compositions are prepared by mixing

the drug, a release controlling agent and possible excipients, and pressing the mixture into matrix tablets, or by coating a core of active ingredient with a release controlling coating so as to obtain coated tablets or granules. Typical release controlling agents include hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, which is commercially available in various types, e.g. Methocel K100LV (m.w. 26,000 g/mol), Methocel K4M (m.w. 86,000 g/mol, Methocel K15M (m.w. 120,000 g/mol) and Methocel K100M. The viscosity of these grades in 2 % water solution (20 °C) is 100 cP, 4000 cP, 15000 cP and 100000 cP, respectively.

The following examples are meant to further illustrate the invention without limitation.

EXAMPLE 1. The stability of formulations of the invention (1 and 2) and reference formulations (1 - 4) are compared in storage conditions.

Formulation 1 (hard gelatine capsule):

Levosimendan	2 mg
Methocel K100LV	46 mg
Alginic acid	23 mg
Avicel PH101	69.5 mg
Stearic acid	1.5 mg

Formulation 2 (pressed tablet):
Levosimendan : alginic acid 1:10

Reference formulation 1 (hard gelatine capsule):

Levosimendan	2 mg
Methocel K4M	35 mg
Avicel PH101	101.6 mg
Stearic acid	1.4 mg

Reference formulation 2 (hard gelatine capsule):

Levosimendan	2 mg
Lactose	197 mg
Magnesium stearate	1 mg

Reference formulation 3 (pressed tablet):
Levosimendan : lactose 1:100

Reference formulation 4 (pressed tablet):

Levosimendan : magnesium stearate 1:1

Formulation 1, consisting of a granule portion and a powder portion, was prepared by mixing Methocel K100LV, alginic acid and levosimendan (1 mg) until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass was dry

granulated by slugging (compressed using a tabletting machine). The compacted mass was sieved and granules of 0.7 – 1.7 mm were collected. For the powder portion, Avicel PH101 and levosimendan (1 mg) was sieved and mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The granule portion and the powder portion and the stearic acid were mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass was filled into hard gelatine capsules no 3.

In Reference formulations 1 and 2 the material was in a powder form. These formulations were prepared by mixing the components until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass was then filled into hard gelatine capsules no 3.

Formulation 2 and Reference formulations 3 and 4 were prepared by mixing the components until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mixture was then pressed into tablets using a conventional tabletting machine.

The stability of the formulations in storage conditions was assessed by determining the level of degradation products of levosimendan in the formulations after storage. The results are given in Table 1.

Table 1. The presence of levosimendan degradation products (OR-1420 and OR-1368) in formulations of the invention (1 - 2) and in reference formulations (1 - 4) after storage. Rh = relative humidity.

	Storage conditions	OR-1420 formed	OR-1368 formed	Number of unknown degradation products
Formulation 1:	9 months 2 - 8 °C	0	0	0
Formulation 2:	8 months 25°C, rh 60%	0	0	0
Ref. formulation 1:	9 months 2 - 8 °C	0.25 %	0.25 %	1, 0.05 %
Ref. formulation 2:	3 months 25°C, rh 60%	1.32 %	0.07 %	5, 0.54 %
Ref. formulation 3:	3 months 25°C, rh 60%	0.75 %	0.23 %	10, 0.93 %
Ref. formulation 4:	7 weeks 25 °C	0	0	1, 1.0 %

Table 1 shows that alginic acid significantly improved the stability of levosimendan formulations in storage conditions as demonstrated by the absence of any degradation products of levosimendan after 8 - 9 months of storage. In contrast, the reference formulations containing no alginic acid show significant formation of levosimendan degradation products.

CLAIMS

1. A pharmaceutical composition comprising levosimendan as an active ingredient and alginic acid as a stability improving agent.

2. A composition of claim 1 wherein the amount of alginic acid is 0.1 - 99 % per weight of the composition.

3. A composition of claim 2 wherein the amount of alginic acid is 5 - 70 %, preferably 10 - 40 %, per weight of the composition.

4. A composition of any of claims 1 - 3, wherein the composition is for oral administration.

5. A composition of claim 4, which is in the form of tablets, dragees, capsules, powders or granules.

6. A composition of any of claims 1 - 5, wherein the amount of the active ingredient in the composition is from 0.1 to 20 % per weight of the composition.

7. A composition of any of claims 1-6 wherein the amount of the active ingredient is 0.1 to 10 mg.

INTERNATIONAL SEARCH REPORT

Int ıtional Application No
PCT/FI 99/00331

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/50 A61K47/36 A61K9/16 A61K9/20 A61K9/28
A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 12135 A (ORION YHTYMAE OY) 23 July 1992 see page 5, line 12-16 & EP 0 565 546 A cited in the application ---	1-7
Y	EP 0 091 767 A (MERCK SHARP & DOHME) 19 October 1983 see abstract ---	1-7
Y	US 4 716 042 A (BLANK ROBERT G ET AL) 29 December 1987 see column 1, line 55-62 ---	1-7
A	WO 98 01111 A (ANTILA SAILA ;HIRVONEN JOUNI (FI); LEHTONEN LASSE (FI); URTTI ARTO) 15 January 1998 ---	1-7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 1999	06/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI 99/00331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 16443 A (LARMA ILKKA ;ANTILA SAILA (FI); HARJULA MAARIT (FI); LEHTONEN LASS) 8 April 1999 see the whole document	1-7

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/FI 99/00331

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9212135 A	23-07-1992	AT	119525 T	15-03-1995
		AU	645399 B	13-01-1994
		AU	1153592 A	17-08-1992
		BG	62002 B	30-12-1998
		BG	97915 A	25-04-1994
		CA	2099262 A	04-07-1992
		CY	1878 A	05-04-1996
		DE	69201640 D	13-04-1995
		DK	565546 T	22-05-1995
		EP	0565546 A	20-10-1993
		ES	2070627 T	01-06-1995
		FI	932618 A	09-06-1993
		FI	972077 A	15-05-1997
		GB	2251615 A,B	15-07-1992
		HK	117395 A	28-07-1995
		HU	64754 A	28-02-1994
		IE	72101 B	12-03-1997
		IL	100553 A	31-12-1995
		IL	114028 A	12-09-1996
		JP	9183767 A	15-07-1997
		JP	2635445 B	30-07-1997
		JP	6504275 T	19-05-1994
		LV	11174 A	20-04-1996
		LV	11174 B	20-12-1996
		NO	300682 B	07-07-1997
		PL	169435 B	31-07-1996
		PL	169415 B	31-07-1996
		SI	9112003 A	31-10-1998
		US	5424428 A	13-06-1995
		US	5569657 A	29-10-1996
		US	5512571 A	30-04-1996
EP 0091767 A	19-10-1983	AT	50492 T	15-03-1990
		AU	555304 B	18-09-1986
		CA	1213217 A	28-10-1986
		DK	146283 A,B,	06-10-1983
		GR	78150 A	26-09-1984
		HK	25091 A	12-04-1991
		IE	56276 B	05-06-1991
		JP	1738086 C	26-02-1993
		JP	4027816 B	12-05-1992
		JP	58190357 A	07-11-1983
		PT	76448 A,B	01-04-1983
		US	4597969 A	01-07-1986
		ZA	8302400 A	28-11-1984
US 4716042 A	29-12-1987	NONE		
WO 9801111 A	15-01-1998	AU	3345997 A	02-02-1998
WO 9916443 A	08-04-1999	FI	973804 A	27-03-1999
		AU	9350698 A	23-04-1999